## REMARKS

### STATUS OF THE CLAIMS

Claims 1, 2, 4-10, 12-15, and 19-22 were pending in this application. Claims 1 and 19 have been amended. Claims 21 and 22 have been withdrawn. Following entry of the amendments, claims 1, 2, 4-10, 12-15, and 19-20 will be pending and at issue.

### SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to add the language "targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule of SEO ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3." Support for this amendment can be found throughout the specification as filed, e.g., support for "the stop codon region" can be found at, e.g., page 6, first paragraph. Support for "not including nucleobases 1608 through 1642 of SEQ ID NO:3" can be found at, e.g., page 82, Table 1, especially data regarding compound comprising SEQ ID NOS:71 and 72, which are complementary to overlapping regions of target SEQ ID NO:3, from nucleobases 1608 through 1627 (SEQ ID NO:71) and nucleobases 1623 through 1642 (SEQ ID NO:72).

Claim 19 has been amended to add the language "differentially inhibits by at least 41%." Support for this amendment can be found throughout the specification as filed, e.g., Example 17 on page 84 of the specification, where embodiments of the compounds claimed by Claim 19 are disclosed, e.g., SEQ ID NOS:16 17, and 18. SEQ ID NOS:16-18 specifically hybridize with and differentially inhibit, e.g., inhibit to a greater degree, the expression of a first variant, TRIP6-I (SEQ ID NO:3) relative to the expression of a second variant, TRIP6-II (SEQ ID NO:11). Support can also be found at , e.g., page 83, line 1-13:

> As shown in Table 1, SEQ ID NOs ... 16, 17, 18, ... demonstrated at least 41% inhibition of human thyroid hormone receptor interactor 6 expression in this assay and are therefore preferred. The target sites to which these preferred sequences are complementary are herein referred to as "active sites" and are

therefore preferred sites for targeting by compounds of the present invention.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

**WITHDRAWAL OF CLAIMS 21 AND 22**

In the 09/23/03 Response Applicant added new claims 21 and 22. In the 02/23/04 Office Action, the Examiner stated that claims 21 and 22 were drawn to different inventions than originally presented and withdrew claims 21 and 22. Without agreeing with the Examiner's argument, Applicant herein withdraws claims 21 and 22.

**OBJECTIONS TO THE CLAIMS**

Applicant acknowledges the Examiner withdrawal of the objections to the claims.

**REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Applicant acknowledges the Examiner's withdrawal of the rejection of claims 1, 2, 4-10, 12-15, and 20 under 112, second paragraph.

The Examiner has maintained her 112, second paragraph rejection of Claim 19 outlined in the 05/21/03 Office Action where **Claim 19** was rejected as allegedly indefinite because of the term "differentially inhibits." The Examiner stated that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of metes and bounds of the term. Claim 19 was also rejected as allegedly indefinite because it is unclear to the Examiner what is meant by "relative to the remaining variants of thyroid hormone receptor interactor 6."

Applicant respectfully disagrees for the reasons presented in the 09/23/03 Response. However, in order to further prosecution, Applicant has amended claim 19 to include the language "differentially inhibits by at least 41%." The additional language "by at least 41%" more clearly defines the term "differentially inhibits." Assays for determining the requisite degree can be found throughout the specifications as found, e.g., at Examples 15 and 17 on pages 80-84 describing antisense inhibition of target expression. Accordingly, one of ordinary skill in

the art would be reasonably appraised of the metes and bounds of the term. Applicant believes that amended claim 19 is not indefinite and requests withdrawal of this rejection.

**REJECTION S UNDER 35 U.S.C. § 102/103**

**Claims 1, 12, 19, and 20** were rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as allegedly anticipated by or obvious over Murthy et al (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667). Applicant respectfully disagrees.

The Examiner has rejected claims 1, 12, 19 and 20 using prior art disclosing an oligonucleotide sequence that is complementary to the target sequence of the instant application. The Examiner states that, since the prior art compound is complementary to the target sequence, the prior art compound "would also be expected to specifically hybridize" to the target and "would then be considered to "inhibit expression" of the gene as claimed, absent evidence to contrary."

Applicant respectfully rebuts the Examiner's prima facie case, providing evidence showing that the prior art compound does not necessarily possess the characteristics of the claimed invention. In addition, Applicant has amended claim 1 to recite a target site of "the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule of SEO ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3." The prior art compound is not complementary to this target site. Applicant amends claim 1 to further prosecution and reserves the right to pursue claim 1 as originally drafted in later prosecution, e.g., in a continuation.

**Examiner's rejection**

The Examiner is rejecting Applicant's claims based on the rationale that every antisense oligonucleotide with 100% complementarity to a target sequence will necessarily both hybridize to and inhibit expression of the target sequence.

In the 02/23/04 Office Action, the Examiner stated that:

> Murthy et al. disclose an oligonucleotide primer of the following sequence: 5'-CTGGAACTGAGAACCCAGCAGGTA-3' (ZRP-R8), see page 20680, last paragraph. This oligonucleotide primer is reverse complementary to nucleobases 1628-1603 of SEQ ID NO:3 of the instant invention. Since the oligonucleotide primer of Murthy et al. meets all the structural requirements of the instant claims, the oligonucleotide primer would also be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively.
>
> Furthermore, since the prior art oligonucleotide primers meets all the structural limitations of the claims, the prior art oligonucleotide primer would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."
>
> Therefore, the instant invention is anticipated or obvious over Murthy et al.

**Applicant's rebuttal**

Applicant believes that, in rejecting the claims under 35 U.S.C. 102 and 103, a prima facie case has been established by the Examiner that can be rebutted by evidence showing that the prior art product does not necessarily possess the characteristic of the claimed product. See, for example, MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195

> USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). ***Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.***

Applicant points out that an oligonucleotide that is complementary to a target sequence does not necessarily inhibit expression of the target sequence. As evidence, Applicant directs the Examiner's attention to Table 1 on pages 81-83 of the instant application. Table 1 shows the results of assaying a set of antisense oligonucleotides (SEQ ID NO:12 to SEQ ID NO:89) for inhibition of target sequence expression. All of the antisense oligonucleotides are complementary to the target sequence. At least five (5) of the antisense oligonucleotides (SEQ ID NOS:36, 37, 38, 44, and 52) are 100% complementary to the target sequence but do not have the function of inhibiting expression of the target sequence.

This data provides evidence that an antisense oligonucleotide with 100% complementarity to a target sequence does not necessarily have the property of inhibiting expression of the target sequence. Therefore, the prior art product disclosed by Murthy does not necessarily possess the characteristics of the claimed invention, e.g., the prior art compound does not necessarily bybridize to and inhibit expression of the target (SEQ ID NO:3).

Applicant reminds the Examiner that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

**Applicant's amendment to Claim 1**

As stated above, Applicant believes that the Examiner's 102/103 rejection of the claims is incorrect. However, in the interest of furthering prosecution, Applicant has amended Claim 1 to recite a target of "the 5'-untranslated region, the start codon region, the coding region, the stop

codon region, or the 3'-untranslated region of a nucleic acid molecule of SEO ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3." The prior art compound cited by the Examiner is not complementary to the target as recited in amended Claim 1, and could not therefore hybridize to the target nor inhibit the expression of the target. Accordingly, the prior art compound does not include each and every element of the claims and Applicant requests withdrawal of this ground for rejection.

**REJECTIONS UNDER 35 U.S.C. § 103**

Applicant acknowledges the Examiner's withdrawal of the rejection of claims 1, 2, 4-10, and 12-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schneider (Forschungszentrum Karlsruhe (2001) FZKA 6587:1-139) in further view of Baracchini et al (US Patent No. 5801154) and Fritz et al (Fritz et al (1997) Journal of Colloid and Interface Science 195:272-288) in view of the fact that the Schneider reference is not prior art. Applicant notes that, in response, Applicant has added the language to claim 1 regarding the "stop codon region" of the target; this region was not included in the amendment of March 10, 2003, when the Examiner maintained that Schneider was available as prior art.

**Claims 1, 2, 19, and 20** were rejected under 35 U.S.C. 103(a) as allegedly obvious over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937). **Claims 4-10 and 12-15** were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937) as applied to claims 1 and 2 above, and further in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Applicant rebuts the Examiner's arguments as drawn to the claims as amended herein. As recited in amended Claim 1, Applicant's invention is a compound targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-

untranslated region of a nucleic acid molecule of SEO ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3, wherein said compound hybridizes to and inhibits expression of the nucleic acid. The invention also includes dependent claims where the compound is an antisense oligonucleotide that has various recited modifications and where the antisense compound is included in various carriers.

Three requirements must be met for a prima facie case of obviousness. First, the combination of prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

**I. The cited combination of prior art references does not teach all of the elements of the claims as amended herein.**

Claim 1 as amended herein claims compounds targeted to the 5'-untranslated region, the start codon region, the coding region, the stop codon region, or the 3'-untranslated region of a nucleic acid molecule of SEO ID NO:3 encoding thyroid hormone receptor interactor 6, with the proviso of not including nucleobases 1608 through 1642 of SEQ ID NO:3. Nowhere does the combination of prior art references cited by the Examiner teach or suggest the target site recited in claim 1 as amended herein. Accordingly, the combination cannot render the claims obvious.

**II. The cited combination of prior art at best provides a generalized incentive insufficient to render obvious the claimed species.**

The combination of art cited by the Examiner also fails to render obvious the rejected claims because the references at best contain a generalized incentive to make antisense molecules against thyroid hormone receptor interactor 6, based on the discovery and characterization of the thyroid hormone receptor interactor 6 protein as taught by Murthy et al and a generalized teaching to make antisense targeted to a "causative gene" as taught by Milligan et al. The cited combination of art at best provides only a generalized incentive to attempt to make antisense compounds against nucleic acid encoding thyroid hormone receptor interactor 6; the cited combination of prior art provides no teaching or suggestion to make the specific antisense

compounds claimed, e.g., compounds directed to the target site as recited in amended claim 1. Baracchini et al. and Fritz et al. do not remedy these deficiencies. The combination therefore fails to make out a prima facie case of obviousness because "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel* 51 F.3d at 1559, 34 USPQ2d at 1216.

Applicant notes that the number of potential inhibitory compounds targeted to thyroid hormone receptor interactor 6 encompasses a vast number of possibilities. As the Federal Circuit held in *In re Baird*, disclosure of a broad genus does not necessarily render obvious each compound within its scope. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Thus, even though the prior art included a polynucleotide sequence encoding thyroid hormone receptor interactor 6 from which potential inhibitory compounds, e.g., antisense oligonucleotides, could be designed, the specific compounds instantly claimed (e.g., those that specifically hybridize and inhibit expression) still would not be obvious given the failure of the prior art to teach or suggest these specific compounds claimed.

**III. Inhibitory oligonucleotide design at the time of the invention was not sufficiently predictable from gene to gene to provide a generic reasonable expectation of success.**

Modifying or combining art to make out a prima facie case of obviousness also requires that the prior art provide an ordinarily skilled artisan working at the time of the invention with a reasonable expectation of success in making the claimed invention. MPEP § 2143.02. Applicant submits that the cited references fail to provide a reasonable expectation of success because the cited references fail to provide direction as to which of many possible choices of thyroid hormone receptor interactor 6 compounds was likely to be successful. As such, the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. *See In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Applicant points out that Milligan et al explicitly teaches a lack of expectation of success: "although the field has progressed over the past decade, recent papers indicate that the observed activity of ODNs in tissue culture may be though non-antisense mechanisms" (page 1923, par.

1); "there are still many inconsistencies with respect to the mechanisms and specificity of antisense ODNs" (page 1930, par. 2); "The task for those striving to develop therapeutic antisense molecules is to design the proper ODN derivatives which have the required properties of stability, affinity, permeation, and, ultimately, favorable pharmacokinetics. None of the currently available ODN analogues contain all of these properties ..." (page 1933, last par.).

In view of the amendments to the claims and the above arguments, Applicant requests withdrawal of this basis of rejection of the claims.

## CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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